(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/13955 A1

(51) International Patent Classification[7]: A61K 47/10, 47/32, 7/48

(21) International Application Number: PCT/US00/08428

(22) International Filing Date: 29 March 2000 (29.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/149,751 19 August 1999 (19.08.1999) US

(71) Applicant: LAVIPHARM S.A. [GR/GR]; Agias Marinas Street, GR-190 02 Peania Attica (GR).

(72) Inventors: FOTINOS, Spiros; 18A J. Statha, GR-106 72 Athens (GR). TSARDAKA, Ekaterini; 12 V. Tsounia Street, Maroussi, GR-151 26 Athens (GR). KOBOROZOS, George; 7 Skousiou Street, Ilioupoli, GR-163 41 Athens (GR).

(74) Agents: SUNSTEIN, Bruce, D. et al.; Bromberg & Sunstein LLP, 125 Summer Street, Boston, MA 02110-1618 (US).

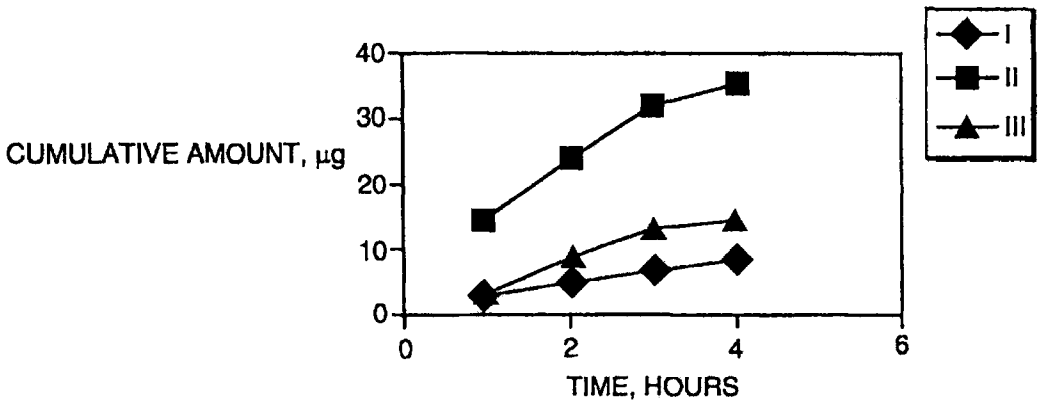
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FILM FORMING POLYMERS, METHODS OF USE, AND DEVICES AND APPLICATIONS THEREOF



(57) Abstract: Compositions and methods for delivering active agents to the skin of subject, including a polymer, an active ingredient and an alcohol are disclosed, the compositions being capable of delivery by rolling, spreading, aerosol or in droplets and of forming a film in contact with the skin.

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FILM FORMING POLYMERS, METHODS OF USE, AND DEVICES AND APPLICATIONS THEREOF

Technical Field

The invention in various embodiments relates to methods and compositions comprising film forming polymers and their applications in pharmaceutics and cosmetics.

Background

Transdermal and topical patches have successfully been used as delivery systems, for administering active substances to the humans either systemically or topically. Transdermal delivery methods have been utilized for the systemic treatment of certain disorders as in U.S. Patent Nos. 5,5152,997; 4,812,313; 4,954,344; and 5,302,395. A transdermal delivery device (patch) containing prostaglandin for the treatment of a pathological condition (e.g. peripheral arterial occlusive disease) is described in U.S. 5,480,648. This patch consists of a pressure sensitive adhesive containing the active component and other additives, laminated onto a backing film. However, the data profile of drug release from this patch as a function of time indicates a process of long term delivery, which is unsuited for the treatment of some conditions for which an effective dose of an active agent is required over a short period of time. Further, a patch for the delivery of active substances, although easy and convenient to use, may present limitations such as sensitization and irritation problems.

Summary

In one embodiment the invention is directed to a composition that includes a mixture of a polymer, an active ingredient, an alcohol, and a beneficial acting active ingredient capable of being preserved within a container such that on release from the container, the composition forms a film on the surface of skin so as to deliver the active ingredient to the skin.

In a further embodiment of the invention, a method for delivering an active agent to the skin of a subject is provided including the steps of combining a polymer, and an active ingredient; adding an alcohol to the mixture to form a composition; and

applying the composition to the skin of the subject for delivery of the active agent to the skin.

Brief Description of the Drawing

Figure 1 is a graph showing on the ordinate the cumulative amount of active component absorbed percutaneously by human stratum corneum, in µg, and on the abscissa the time in hours that the sample was taken for analysis following application to the stratum corneum, formulated in (I) a commercial product (SYNERGIE patch containing 0.73% salicylic acid, Lavipharm S.A. for Garnier, France; (II) a dry film produced by a formulation applied and dried in situ containing 3.23 % salicylic acid; and (III) the formulation identical to (II) applied as a liquid.

Detailed Description of Specific Embodiments

A new formulation and method for the delivery of active substances to human subjects as a quick drying film forming gel may overcome the problems of slow release, and of sensitization and irritation associated with transdermal topical patches.

In one embodiment, the formulation of the invention includes a film- forming material wherein the film is formed upon application of the formulation to a selected site of the human body. In a preferred embodiment of the present invention the specific formulation can form a film when applied to the skin. The composition can be manufactured as a commercial product in an appropriate device/apparatus for application of the composition to the skin of the subject. The amount of the composition that is delivered by the device to the skin can contain an effective amount of the one or more of the active substances in the composition. The composition may also include a beneficially acting agent that possesses multifunctional properties such as glycerol, lanolin, vaseline, and the like. The film is formed directly on the site of application after the composition is sprayed or otherwise applied, and when dry the gel forms a film on the skin.

The film can be easily removed with water or can be peeled off. Active ingredients to be delivered through such a means can be any of a pharmaceutical or a cosmetic agent. In various embodiments, an active agent can be an anti-inflammatory, a local anesthetic, a xanthine derivative, an antihistaminic, an antifungal, an

antimicrobial, an antibiotic, a cardiovascular agent, a hormone, an agent for the treatment of erectile dysfunction, a vasodilator, an analgesic, an antirheumatoid, a chemotherapy agent, an adrenergic agonist or antagonist.

In another embodiment, an active agent in a formulation of the invention can be an antioxidant, a moisturizing agent, an anti-hyperpigmentation agent, an anti-blotching agent, an anti-aging agent, an anti-collagenase substance, a free radical scavenger, a seboregulator, an hydrative, a keratolytic agent and an α- or β- hydroxy acid. A formulation can include a combination of two or more active agents. An ingredient can have multiple different functions in a composition, for example, an emollient such as glycerol can also confer desirable physical properties.

In yet another embodiment, an active agent can be any of a variety of wound healing agents.

The formulations and compositions of this invention can be applied both to the skin and the mucosa.

Definitions

As used in this description and in the accompanying claims, the following terms shall have the meanings indicated unless the context otherwise requires.

An embodiment of the formulation contains a polymer, for example, a polyvinyl alcohol (PVA), for example, a mixture of polyvinyl alcohol A and polyvinyl alcohol B (DuPont, Wilmington, DE). Other biocompatible polymers which are biologically inert polymers include cellulose, carboxymethyl cellulose, PVP/polyvinyl propylene, polyurethane, ethylene vinyl acetate, or copolymers thereof (U.S. Patent No. 5,925,372). A preferred polymer is a polyvinyl alcohol, which confers sufficient viscosity to the composition so that it can form a film, which upon evaporation and concentration of the solvent can form a film that adheres to the skin. For convenience, a solution or mixture containing the polymer is referred to in the Tables herein as "A". However the methods and processes for preparation of the polymer and other components of the formulations herein are not thereby limited by order of addition or dissolution of ingredients, or by formulation in particular combinations of ingredients, by use herein of this nomenclature.

An "active ingredient" or agent is a substance that presents specific properties used for the treatment of a particular condition. These active agents can be pharmaceutical agents, cosmetics, or wound healing agents.

A "beneficially acting agent" is used mainly in a cosmetic formulation and are not considered to be directed to the treatment of a particular condition, but possesses multifunctional properties that can contribute to the improvement of a condition. For example, glycerol (glycerin) can be included in a moisturizing cream (having a specific moisturizing agent) as an excipient, and in addition the glycerol contributes and enhances the moisturizing properties of the cream.

An embodiment of the formulation contains an active ingredient or agent, more particularly, an solution or mixture of one or more pharmaceutical, wound healing, and/or cosmetic active ingredients, and can include additional materials such as ethanol, propylene glycol, butylene glycol, and/or other components. The active pharmaceutical ingredients can include an anti-infective, for example, an anti-viral agent, an anti-bacterial agent, an anti-fungal agent, or an anti-parasitical agent. An anti-bacterial agent such as chlorhexidine digluconate, or Triclosan (an antiseptic agent, Irgasan DP 300, Ciba Chemicals), and a salt such as zinc acetate, and other components which can be a pharmaceutical or a cosmetic agent, are listed in the Tables. For the purpose of convenience, the solution or mixture having the one or more active ingredients can be referred to as "B" in the Tables and in the text. The method of preparation of the formulations herein are not thereby limited by this designation with respect to order of dissolution or addition of components.

The active ingredient can optionally be formulated in an alcohol solvent, more particularly a lower alkyl alcohol (lower alkanol), for example, methanol, *n*-propanol, *I*-propanol, more preferably ethanol, or an alcohol solution or suspension, preferably an ethanol solution or suspension. Active ingredients such as salicylic acid. sodium disulfite, and dl-α-tocopherol can be prepared in the alcohol. For convenience, a formulation can be prepared using only two mixtures or solutions in which the active ingredient in an alcohol solvent is referred to as "B" (see Tables 3, 5, and 6). A single

solution can be used, for example an aqueous solution, in which case a designation for the solution or mixture is not given (see Table 7).

One or more hydrophobic substances can be included in the formulation, for example, a formulation to be used in wound healing such as a fumed silica and the like, to modify the release and skin flux characteristics of the formulation system. Other hydrophobic ingredients can be incorporated in the compositions for their multi-functional properties in skin care, for example, Dermacryl 79 (a high molecular weight carboxylated acrylic polymer) by National Starch & Chemical Ltd., U.K., to be used as an effective occlusive agent in the retention of moisture within the skin, and/or to modify the release and skin flux characteristics of the system.

Contained in the formulation embodiments of the present invention can be additives such as solvents, plasticizers, solubilizers, emollients, and preservatives known in the art to be suitable for topical application.

The formulations can be prepared for delivery by use of any of a variety of devices, such as a rollette applicator, a jar having an apical manual pump, an atomizer, or directly from a tube or bottle. A "rollette" applicator is a ball-tipped container such as is commonly used for application of deodorant. A "jar having an apical manual pump" includes a container capable of using compressed air produced by manual depression and release of a movable piston, which imparts to the compressed air a volume of the composition described herein for delivery to the skin of the subject. A "tube" is a compressible delivery container having a cap or cover, such as is typically used for delivery of topically active agents and toothpastes.

Delivery of a controlled dosage of an embodiment of the invention which is a composition can be assisted with an adhesive patch which is a border for a non-patch portion, the non-patch portion having a specific area, for delivery to that specific area of skin. The patch can be of any shape, for example round or rectangular, and the proportion of the border to the non-patch interior is selected by one of skill in the art of design of adhesive patches, to remain in place for a limited period of time following application by any of the devices above. The non-patch interior may have an area of one to 5 sq. cm, or 0.2 to one sq. cm, which are guidelines only and are not to be

construed as limiting. The patch is attached to the skin or mucosa of the particular location of skin to be treated, and the composition is applied to the non-patch portion of exposed skin, for example, by spraying or spreading; the patch can be removed when the composition has dried to form a film, or can remain in place.

"Skin" shall mean all of an intact epidermis, a tissue exposed by surgery, a mucosal surface such as an epidermal surface in an oral or vaginal cavity or on a glans penis, and a wound tissue created by abrasion, burn, incision, or a projectile. Cleansing of wounds using a spray has been shown (U.S. Patent No. 5,059,187), however the spray being delivered as shown in this art was not shown also to form a film. "Mucosa" shall mean the moist epithelial tissues, including for example, the oral or vaginal cavities and glans penis.

Preparation of the composition

In one embodiment, the preparation of the gel comprises mixing the ingredients designated as B with those designated as A, as so designated in the Tables, under a condition of continuous agitation. To this mixture the ingredients designated as C are added. The preparation is maintained in a sealed container for a period of time, for example, for approximately 6-18 hours, for example, for 12 hours, to allow for removal of the air bubbles. Air bubbles can form and rise to the upper surface of the liquid under conditions of ambient pressure and temperature. Removal of air bubbles from the liquid can be accelerated by application of decreased atmospheric pressure or increased temperature, under conditions of pressure and temperature that are compatible with maintenance of the activity and stability of the composition.

The methods and compositions of the present invention are useful for delivery of one or more of a pharmaceutical agent, for example, an anaesthetic agent, an anti-inflammatory agent such as a glucocorticosteroid and a non-steroidal anti-inflammatory agent (NSAID), or for delivery of one or more of a cosmetic agent, or for delivery of a combination of two or more pharmaceutical and/or cosmetic agents.

Examples of an anaesthetic agent include Suprane® (desflurane, Ohmeda), Versed® (midazolam hydrochloride, Roche), Duronest® (etidocaine hydrochloride, Astra), Naropin® (ropivacaine hydrochloride, Nesacaine® (chloroprocaine

hydrochloride), and Xylocaine® (lidocaine hydrochloride). Base forms of the anaesthetic agents can be incorporated into a composition; for example, lidocaine base in Example 11 herein.

Examples of a glucocorticosteroid agent include Celestone® (betamethasone sodium, Schering), Cortone® acetate (cortisone acetate, Merck), Decadron® (dexamethasone sodium phosphate, Merck), and Hydrocortone® (hydrocortisone, Merck).

Examples of an NSAID agent include Toradol® (ketorolac tromethamine, Roche), Cataflam® (diclofenac potassium), Clinoril® (sulindac, Merck), Indocin® (indomethacin sodium trihydrate, Merck), and Lodine® (etodolac, Wyeth-Ayerst).

A cosmetic agent can include, for example, an anti-irritant such as: α-bisabolol, camomile extract, tea tree (*Melaleuca alternifolia*) oil, green tea (*Camellia sinensis*) extract, aloe (*Aloe vera*) extract (NOVA; see Examples 1-6), licorice (*Glycerrhiza glabra*) extract, glycyrrhetinic acid, witch hazel (*Hamamelis virginiana*) extract, and glycerol. Green tea and other plant material extracts can be obtained, for example, in solution with propylene glycol and water, for example, Optivegetol Green Tea P108 Hydro, Gattefosse (France); Optivegetol Cinnamon (*Cinnamomum cassia*) P110 Hydro, Gattefosse; and Optivegetol Guarana (*Paullinia cupana*) P107 Hydro, Gattefosse. Optivegetol green tea hydroglycollic extract possesses anti-inflammatory and anti-irritant properties.

Examples of anti-infective agents include: anti-viral , anti-bacterial, anti-fungal and anti-parasitic agents. Anti-bacterial agents include chlorhexidine and Triclosan. Anti-infectives may further include antiseptic agents. Examples of an antiseptic agent include: an alcohol such as a lower alkyl alcohol including ethyl alcohol and isopropyl alcohol. Other antiseptic agents include phenyl alcohol, tea tree oil, iodine compounds such as povidone iodide, and mercurichrome.

Examples of an antioxidant agent are propyl gallate, sodium bisulfite, ascorbic acid (vitamin C) and ascorbic acid esters, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), vitamin E, and cysteine.

Examples of a vitamin include: vitamin A, vitamin A palmitate, β-carotene, ascorbic acid (vitamin C), ascorbyl palmitate, tocopherol (vitamin E), tocopheryl acetate (vitamin E acetate), vitamin K, and vitamin F (glyceryl linoleate and glyceryl linolenate).

Examples of a skin-conditioning ingredient include: extract of any of aloe (for example, *Aloe vera*), *Camellia sinensis* (green tea), camomile, cucumber, corn flower, orange peel, dog rose hip; marine extracts such as those from seaweed, kelp, and algae; rice bran oil, wheat germ oil, avocado oil and almond oil; an α-hydroxy acid (AHA) such as glycolic acid, lactic acid, malic acid, and citric acid; a β-hydroxyl acid such as salicylic acid, a polymeric hydroxylic acid, and a ketoacid; and a β-glucan, panthenol, an anthocyanidin, a phytic acid, and an amino acid such as glycine, proline, lysine and leucine.

In embodiments of the present invention, a cosmetic active agent known in the art may be incorporated in the film forming compositions for improving skin appearance. These agents can be any of anti-hyperpigmentation, anti-blotching, anti-aging, eye contour, slimming, anti-cellulite, soothing/sunburn, anti-irritating, skin firming and lifting, anti-elastase and anti-collagenase substances, free radical scavengers, seboregulators, hydratives, vitamins, AHA products, anti-oxidants and minerals.

Anti-hyperpigmentation agents typically used for counterbalancing this condition can include tyrosinase inhibitors such as peptide mixtures and plant extracts, fermentation products, and antioxidants such as hydroquinone (see Examples 7-8), kojic acid (see Example 9), ascorbic acid derivatives, synthetic or natural derivatives of hydroquinone and hydroquinone precursors. Gatuline whitening obtained by fermentation of kojic and lactic acids, is a tyrosinase inhibitor. In preferred embodiments of the invention, anti-hyper pigmentation agents are Melawhite of Pentharm Ltd., Basel, Switzerland; Biowhite™ of Coletica, France; Etioline of Sederma, France; Arbossa of Kelesima, Italy; Gatuline whitening of Gattefosse, France; Ascorbocilan C of Exsymol, Monaco; and Kojic acid of Alps Pharm., Japan.

Anti-blotching agents typically used for counterbalancing this condition can include saponines and caffeic acid containing plant extract and related compounds. Preferably in the present invention, anti-couprose agents include Gatuline A of Gattefosse, France, and Ivy-Phytelenes of Sepex, France.

Anti-aging agents include glycosaminoglycan derivatives such as chondroitin sulfate and ATP; other bioactivators such as farnesol and farnesol derivatives; panthenol and panthenol derivatives; beech tree bud extracts; and soya bean embryonic tissue extracts and related compounds. Preferably in the present invention, anti-aging agents are Unichodrin ATP and Unitrienol T-27 (Induchem, Switzerland), and Gatuline RC (Gattefosse, France).

Skin firming and lifting agents include a mixture of plant protein fractions, flavonoids and tannins such as Gatuline Lifting of Gattefosse, France.

Keratolytic agents include salicylic acid, benzoyl peroxide, sulfur, retinoic acid, and any of several fruit acids.

Free radical scavengers include synthetic pseudopeptides resistant to hydrolysis such as Carcinine hydrochloride; lipoamino acids such as L-lysine lauroylmethionine; plant extracts containing multi-enzymes; and natural tocopherol and related compounds. In a preferred embodiment of the invention, free radical scavengers are Alistin of Excymol, France, Lipacide LML of Seppic, France, and Radicallne® of Coletica, France.

Seboregulators include lipoamino acids of natural origin such as capryloyl glycine; oxidative enzyme mixtures; and mixtures of hydrolyzed yeast proteins and vitamins and related compounds. In a preferred embodiment of the invention, seboregulators are Asebiol® BT of Laboratoires Serobiologiques, France; Lipacide C8G of Seppic, France; Sebomine/SB12 of Sederma, France; and Biomeris of Biopole, Belgium.

AHA specific products can be mono-, di-, tri-hydroxy acids of natural origin, which may further be linked to polysaccharides or proteins. In a preferred embodiment of the invention, AHA specific products are Glycacid® and Protacid® of Coletica,

France; Multifruit® BSC of Brooks Industries Inc., USA; Amidroxy of Alban Mulle Int., France; and AHA extracts of Phytochim, France.

Additional agents that can be present in the compositions of embodiments herein include Crolastine 30 which contributes to elasticity of the skin, Hygrocomplex ARO which is a moisturizing agent, Crodalan (Croda, England), and Biopure 100 which is a preservative (see Table 1).

EXAMPLES

Delivery

Each formulation can be sprayed upon the skin by any of the methods known in the art, for example, delivering a measured dose using a spray container (see U.S. Patent Nos. 5,618,515 and 5,769,283) as an atomizer attached to a reservoir, or for example, a pump inserted into the aqueous solution such that removal of a restraining cap enables use of first and second fingers to stabilize the vessel containing the reservoir while pushing with the thumb causes delivery of the measured dose. Use of an atomizer does not require pressurization of an additional gas component. The geometry of the relationship of the pump and the reservoir containing the gel can be of standard description, for example, a separate squeezable pump removably attached to one side, or a top pump which is activated by a push mechanism.

Ranges of Components

Mixture or solution A can comprise polyvinyl alcohol A in a range from 5 to 10% amount, on a wet basis, with respect to the total composition. This component is preferably present at less than 20%, more particularly 1-10%, more particularly from 6 to 8%, more preferably from 6.9 to 7.5%, on a wet basis, with respect to the total composition. Polyvinyl alcohol B is present at less than 20%, more particularly 1-10%, more particularly from 3.5 to 6.0%, preferably from 4.0 to 5.0%, more preferably from 4.5 to 4.8%, on a wet basis, with respect to the total composition. The ratio of polyvinyl alcohol A:polyvinyl alcohol B ratio is about 3:2. Solution or mixture A

generally comprises 50 to 60% of the total composition, preferably 52 to 59% of the composition, on a wet basis, with respect to the total composition.

Mixture or solution B can comprise active ingredients and water. Humectant ingredients which are miscible with water, such as propylene glycol can be added, as can other solvents such as ethanol. Examples of active ingredients in B are found in Tables 1 and 2. Active ingredients can be present, on a wet basis, with respect to the total composition, in amounts from 0.01 to 2.0%, for example, from 0.1 to 6%.

Mixture or solution A can comprise an alcohol of a lower alkyl (a lower alkanol), for example, methanol, *n*-propanol, *I*-propanol, preferably ethanol, and one or more additional ingredients, which preferably are more soluble in ethanol compared to water. The alcohol can be present from 5 to 20% on a wet basis, with respect to the total composition. The alcohol, preferably ethanol, is preferably present at 8 to 18%, 10 to 16%, most preferably 12 to 17%, on a wet weight basis with respect to the total composition. An active ingredient soluble in the alcohol such as hydroquinone, salicylic acid, and/or dl-α-tocopherol, can be present in C. The active ingredient in C can be present from 0.01 to 10%, preferably 0.1 to 1%, on a wet basis, with respect to the total composition.

Examples 1-32. Formulations of active components in film forming polymers

The cosmetic formulations of Examples 1-6 are shown in Table 1, and formulations containing anti-pigmentation agents are shown in Examples 7-9 in Table 2. Except for Example 9, all of the components are mixed as described above.

Examples 7-9 (Table 2) are formulations of the invention having anti-pigmentation agents. Examples 7 and 8 contain hydroquinone, which can be applied topically as a depigmenter agent (Merck Index, Tenth Ed., 1983, Rahway, NJ). The formulation for Example 9 contains anti-pigmentation agents Melfade™, GATULINE® whitening, Kojic acid, and Biowhite™. A formulation for treating age spots, for example on the hands, face, shoulders, chest or neck, is shown in Example 10 (Table 3). The methods and compositions that are gel forming polymers are particularly suitable for application to a limited surface area of skin such as an age spot.

The invention in another embodiment is a formulation containing a local anesthetic (Example 11, Table 4), for example, the anesthetic lidocaine. In yet another embodiment, the invention provides a formulation containing an anti-histaminic agent, hydroxyzine (Examples 12-15, Table 5). The methods and compositions of the invention are suitable to treatment of limited areas of skin having an inflammation or irritation, such as an allergic contact dermatitis, or a reaction to an insect bite, by application of a film-forming gel having a water soluble polymer and containing an active agent such as an anesthetic or antihistamine.

The compositions of the invention can include an animal protein hydrolysate, for example, a collagen extract, as a skin conditioning agent (Examples 16-19, Table 6).

An anti-acne agent can combine one or more of each of an anti-irritant, antibacterial agent, and a keratolytic agent such as salicylic acid (Examples 20-22, Table 7). Additional formulations (Examples 23-29) are shown in Table 8, the formulations having an anti-bacterial agent such as chlorhexidine, triclosan, or both. Additional formulations of Examples 30-32 are shown in Table 9.

Table 1. Compositions of cosmetic formulations for Examples 1-6

Mix	Component	%Amount (on a wet basis)					
		Ex.1	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6
A	Polyvinyl alcohol A	7.04	7.30	7.30	7.30	6.99	7.30
	Polyvinyl alcohol B	4.53	4.70	4.70	4.70	4.50	4.70
	Deionized water	58.05	54.20	52.20	58.20	57.61	60.20
B	Aloe vera gel NOVA[1]	1.93	2.00	2.00	2.00	1.91	
	Crolastine 30[2]						2.00
	Deionized water	6.22	6.45	6.45	6.45	6.17	6.25
	Propylene glycol						4.00
	Hygrocomplex ARO[3]						2.00
	Crodalan[5]						0.20
	Butylene glycol		4.00	4.00	4.00		
	Chlorhexidine digluconate	0.19	1.00	1.00	1.00	0.96	
	Optivegetol[4]	5.79	6.00	6.00		5.74	
	Zinc acetate			2.00	2.00		
	Biopure 100[6]	0.24	0.25	0.25	0.25	0.24	0.25
C	Nipagin M[7]	0.10	0.10	0.10	0.10	0.10	0.10
	Salicylic acid	0.96	1.00	1.00	1.00	0.96	
	Ethanol absolute	14.95	13.00	13.00	13.00	14.83	13.00

[1]Aloe vera gel NOVA, a juice (gel) from fresh leaves of the *Aloe vera* plant, possesses anti-nflammatory and anti-irritant properties.

[2]Crolastin 30 is a hydrolyzed elastin, contributing to elasticity of the skin.

[3]Hygrocomplex ARO, a mixture of specific amino acids, forms a natural moisturizing factor (NOVAROM, Hannover, Germany).

[4]Optivegetol, a hydroglycolic extract of green tea leaves, has free radical scavenging, antioxidant, and vitamin P properties (Gattefosse, France).

[5]Crodalan is a multi-functional surface active emollient (Croda, England).

[6]Biopure 100 (imidazolidine urea) is a preservative for cosmetic and dermopharmaceutical formulations (NIPA Lab, U.K.).

[7]Nipagin M, a methyl 4-hydroxybenzoate solution, is used as preservative (NIPA Lab, U.K.).

Table 2. Compositions for Examples 7-9 containing anti-pigmentation agents

Mix	Component	%Amount (on a wet basis)		
		Ex.7	Ex.8	Ex.9
A	Polyvinyl alcohol A	7.50	7.50	7.30
	Polyvinyl alcohol B	4.70	4.70	4.70
	Sodium disulphite	0.10		
	Melfade™ [1]			5.00
	Deionized water	58.80	56.80	55.90
B	Aloe vera gel	2.00	2.00	
	Deionized water	6.45	6.45	
	Propylene glycol	4.00		
	Optivegetol		6.00	
	Biopure 100	0.25	0.25	
	GATULINE ® whitening[2]			5.00
	Kojic acid			1.00
	Biowhite™ [3]			0.10
	Eutanol G16S			2.00
	Butylene glycol			2.00
	Nipagin M			0.10
	Ethanol absolute			16.90
C	Nipagin M	0.10	0.10	
	Oxynex 2004[4]	0.10	0.10	
	Sodium disulphite		0.10	
	dl-α-tocopherol	1.00	1.00	
	Hydroquinone	2.00	2.00	
	Ethanol absolute	13.00	13.00	

[1]Melfade™ is a tyrosinase inhibitor by Pentharm, Basel, Switzerland.
[2]GATULINE® whitening is a tyrosinase inhibitor containing a fraction obtained by fermentation (kojic acid and lactic acid), licorice extract, and TRANSCUTOL® (Gattefosse, France).
[3]Biowhite™ is a tyrosinase inhibitor (Coletica, France).

[4]Oxynex 2004 is an antioxidant mixture used in pharmaceuticals, containing 20% butyl hydroxy toluene, 10% ascorbic acid, and 10% citric acid in glyceryl stearate and propylene glycol (E. Merck, Germany).

Table 3. A composition of Example 10 containing anti-aging spot agents

Mix	Component	%Amount (on a wet basis)
A	Polyvinyl alcohol A	7.50
	Polyvinyl alcohol B	4.70
	Sodium disulphite	0.10
	Deionized water	58.80
B	Aloe vera gel	2.00
	Deionized water	6.45
	Propylene glycol	4.00
C	Nipagin M	0.10
	Oxynex 2004	0.10
	dl-α-tocopherol	1.00
	Hydroquinone	2.00
	Ethanol absolute	13.00

Table 4. A composition of Example 11 containing a local anesthetic

Mix	Component	%Amount (on a wet basis)
A	Polyvinyl alcohol A	7.3
	Polyvinyl alcohol B	4.70
	Deionized water	62.1
B	Propylene glycol	5.0
	Lidocaine base	5.0
	Ethanol absolute	15.9

Table 5. Compositions containing hydroxyzine hydrochloride (antihistaminic) of Examples 12-15

Mix	Component	%Amount (on a wet basis)			
		Ex.12	Ex. 13	Ex.14	Ex.15
A	Polyvinyl alcohol A	7.3	7.3	7.3	7.3
	Polyvinyl alcohol B	4.7	4.7	4.7	4.7
	Deionized water	65.9	51.0	51.0	51.0
B	Hydroxyzine HCl	5.0	5.0	5.0	5.0
	Linoleic acid				5.0
	Montane 80 VGA			5.0	
	Eutanol G16S		5.0		
	Butylene glycol	4.0	10.0	10.0	10.0
	Nipagin M	0.1	0.1	0.1	0.1
	Ethanol absolute	13.0	16.9	16.9	16.9

Table 6. Compositions of Examples 16-19 containing collagen

Component	%Amount (on a wet basis)			
	Ex.16	Ex. 17	Ex.18	Ex.19
Polyvinyl alcohol A	7.3	7.3	7.3	7.3
Polyvinyl alcohol B	4.7	4.7	4.7	4.7
Deionized water	72.98	74.98	74.97	75.58
Hydrolyzed collagen[1]	0.6	0.6	0.6	0.2
Glycerol	2.0	2.0	2.0	
Potassium sorbate	0.12	0.12	0.12	0.12
Germal II[2]	0.3	0.3	0.3	0.3
MEM-EARL[3]	12.0	10.0	10.0	10.0
Benzalkonium chloride			0.1	

[1]Hydrolyzed collagen is a collagen extract used as a skin conditioning agent (Croda, Inc.).
[2]Germal II is diazolidinyl urea preservative (ELTON, Greece).
[3]MEM-EARL is a tissue culture medium (Sigma, St. Louis, MO).

Table 7. Compositions of Examples 20-22 containing anti-acne agent salicylic acid

Mix	Component	%Amount (on a wet basis)		
		Ex.20	Ex.21	Ex.22
A	Polyvinyl alcohol A	6.89	7.3	7.3
	Polyvinyl alcohol B	4.43	4.7	4.7
	Deionized water	60.57	53.2	61.7
B	Aloe vera gel NOVA	1.89	2.0	2.0
	Deionized water	6.08	6.45	6.45
	Butylene glycol		4.0	
	Chlorhexidine digluconate	0.94	1.0	1.0
	Optivegetol	5.66	6.0	
	Biopure 100	0.24	0.25	0.25
C	Nipagin M	0.09	0.1	0.1
	Salicylic acid	0.94	1.0	1.0
	Ethanol absolute	12.26	13.0	15.5

Table 8. Compositions of Examples 23-29 containing anti-bacterial agents

Mix	Component	%Amount (on a wet basis)						
		Ex.23	Ex.24	Ex.25	Ex.26	Ex.27	Ex.28	Ex.29
A	Polyvinyl alcohol A	6.91	6.98	7.01	7.12	6.88	6.87	6.85
	Polyvinyl alcohol B	4.45	4.49	4.51	4.58	4.43	4.42	4.41
	Deionized water	56.95	57.54	57.83	58.73	56.73	56.67	56.45
B	Aloe vera gel NOVA	1.89	1.91	1.92	1.95	1.88	1.88	1.88
	Deionized water	6.10	6.16	6.20	6.29	6.08	6.07	6.05
	Butylene glycol	1.89	1.91	1.92	1.95	1.88	1.88	1.88
	Chlorhexidine digluconate	1.49	1.51	1.52		1.49	1.49	1.48
	Glycerol					1.88	1.88	1.88
	Biopure 100	0.24	0.24	0.24	0.24	0.24	0.24	0.23
C	Nipagin M	0.10	0.11	0.11	0.11	0.10	0.10	0.10
	Glycyrrhetinic acid						0.10	
	Salicylic acid	2.01	1.00	0.50	0.50	0.50	0.50	1.00
	Triclosan	0.30	0.31	0.31	0.31	0.30	0.30	0.30
	Montane 80 VGA	2.50	2.52	2.54	2.58	2.49	2.49	2.48
	Bisabolol	0.50	0.51	0.51	0.52	0.50	0.50	0.50
	Ethanol absolute	14.67	14.81	14.89	15.12	14.61	14.59	14.53

Table 9. Compositions of Examples 30-32 containing anti-bacterial agents

Mix	Component	%Amount (on a wet basis)		
		Ex.30	Ex.31	Ex.32
A	Polyvinyl alcohol A	6.84	6.74	6.64
	Polyvinyl alcohol B	4.40	4.34	4.27
	Deionized water	56.39	55.60	54.74
B	Aloe vera gel NOVA	1.87	1.85	1.82
	Deionized water	6.04	5.96	5.86
	Butylene glycol	1.87	1.85	1.82
	Chlorhexidine digluconate	1.48	1.46	1.44
	Glycerol	1.87	1.85	1.82
	Biopure 100	0.23	0.23	0.23
C	Nipagin M	0.10	0.10	0.10
	Dermacyl 79		1.50	3.00
	Glycyrrhetinic acid	0.10		
	Salicylic acid	1.00	0.49	0.50
	Triclosan	0.30	0.30	0.29
	Montane 80 VGA	2.47	2.44	2.40
	Bisabolol	0.50	1.00	0.98
	Ethanol absolute	14.52	14.31	14.09

Example 33. Pre-clinical data showing efficacy of formulations to heal acne symptoms

The efficacy of formulations of the present application was tested on volunteer humans aged 20 to 34 years. The formulations investigated were those of Examples 28, 29, 30 and 31, respectively.

Using an appropriate applicator system, each formulation was applied exclusively at the site of an inflamed area (the acne-related inflammation) of the face, and remained in place overnight. Application was repeated on each of subsequent nights, until complete healing was observed.

The results in the following tables are given as the percentage of subjects cured as a function of time, expressed as the number of nights of use. The effectiveness of each of the formulations was evaluated using the following criteria: increase in dryness of the inflamed area, reduction of erythema, and reduction of edema.

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Table 10. Effect on dryness (significant improvement)

Application:	first	second	third	fourth
Example 27		50	50	
Example 28		20	20	60
Example 29				100
Example 30	34	66		

Table 11. Reduction of inflammation (significant improvement)

Application	first	second	third	fourth
Example 27		50	50	
Example 28	40		60	
Example 29		100		
Example 30				66*

* Moderate improvement. One subject did not complete the study

Table 12. Reduction of edema (significant improvement)

Application	first	second	third	fourth
Example 27	50	50		
Example 28	20	20	40	
Example 29		100		
Example 30	66*			

* One subject did not complete the study

Tables 10-12 show that each of the formulations of Examples 28-31, when applied using the methods of the invention to form a gel to deliver the active agents to the skin of the subject, was effective as an anti-acne agent, by the three criteria of

increasing the dryness, reducing erythema (redness), and reducing edema (swelling), within four nights of use. Some of these formulations successfully met one or two of the criteria after only two to three nights of use. The formulation of Example 28 eliminated inflammation and edema after two nights, and provided a dry area after three nights of use. The formulation of Example 33 eliminated edema after one night, produced dry skin after two nights, and reduced inflammation after the fourth night of use.

Example 34. Evaluation of the formulations using a depletion analysis

Formulations herein were evaluated for capacity to release active substances as a function of time after topical application to human skin. To determine the rate and extent of release of an active component of compositions of the formulations, a patch depletion analysis was performed. Among formulations of embodiments of the invention herein, those of Examples 24, 25, and 31 were tested.

An appropriate amount of each composition was applied to the hand (covering the upper side), and dried to form a film. At 45 and 120 minutes post application, a portion of the film was removed using forceps, and the amount of active components was determined by employing HPLC-based analytical procedures.

The results shown in the Table 13 express the percent of salicylic acid remaining in the patch sample, calculated from comparison to the amount at time zero (100%). The data demonstrate that the amount of salicylic acid in the film patch decreases as a function of time that the film of each of formulations has been in contact with skin of the hand.

These data indicate that significant amounts of the original content of an active component was depleted from the gel composition during the time that the gel film was in contact with the skin, since the depleted amount increased as a function of time. In this test, the formulation of Example 31 delivered a greater proportion of the active component to the skin of the human hand than the other formulation during an application period of 2 hours.

Table 13. Depletion of active ingredient from gel patches as a function of time of skin contact

Formulation	Time of sample (min)	salicylic acid remaining (%)
Example 24	45	61.1
	120	51.9
Example 25	45	67.5
	120	66.0
Example 31	45	71.6
	120	44.1

Example 35. Evaluation of percutaneous absorption using formulations

To evaluate any local effect induced by the use of the formulations, the absorption (flux) of active component salicylic acid from the formulation shown in Table 14, was determined in vitro by using human cadaver skin by the method of Franz, T. (Percutantous absorption on the relevance of the in vitro data, J. Invest. Derm. 64:190-195(1975)). For these in vitro flux studies, stratum corneum samples of human skin obtained from fresh post-mortem cadaver autopsy was used. Samples of stratum corneum were separated according the Kligman, A. M. et al. (Preparation of the isolated sheets of the human stratum corneum, Arch. Derm. 88:702 (1963)). The formulation of Table 14 was pre-dried to form a film prior to application onto the Frantz device, having an area of 0.639 cm^2. Another aliquot of same amount of the formulation was placed in liquid form onto the surface of the cell in the Frantz device.

Observation of the skin flux (percutaneous absorption) for each sample at each time point (expressed as cumulative amount of salicylic acid permeation per unit of area at any given time) was compared as a function of time in each of the following compositions: (I) commercial product (SYNERGIE patch from Lavipharm S.A., for Garnier, France) containing salicylic acid as active ingredient, 0.73% w/w on a dry basis; (II) a dry film of the formulation in Table 14; and (III) the identical liquid formulation of Table 14 before dryness, both II and III containing the same amount of salicylic acid, 3.23% w/w on a dry basis.

The results (Fig. 1) show that significant amounts of the active component permeated into the stratum corneum. The greatest flux of the active component was observed with use of the dry gel (II in Fig. 1), a formulation which is an embodiment of the invention.

Table 14. Formulation for percutaneous absorption study of Example 35

Mix	Component	% Amount (on a wet basis)
A	Polyvinyl alcohol A	6.87
	Polyvinyl alcohol B	4.42
	Deionized water	56.62
B	Aloe vera gel NOVA	1.88
	Deionized water	6.07
	Butylene glycol	1.88
	Chlorhexidine digluconate	1.49
	Glycerol	1.88
	Biopure 100	0.24
C	Nipagin M	0.10
	Salicylic acid	0.70
	Triclosan	0.30
	Montane 80 VGA	2.48
	Bisabolol	0.50
	Ethanol absolute	14.67

What is claimed is:

1. A composition, comprising:

a mixture of one or more of a polymer, an active ingredient, an alcohol and a beneficial acting active ingredient capable of being preserved within a container such that on release from the container, the composition forms a film on the surface of skin so as to deliver the active ingredient to the skin.

2. A composition according to claim 1, wherein the preserved mixture is a gel.

3. A composition according to claim 2, wherein the gel dries on the skin so as to form a film .

4. A composition according to claim 1, wherein the active ingredient is selected from the group consisting of one or more of a pharmaceutical agent, a wound healing agent, and a cosmetic agent.

5. A composition according to claim 1, wherein the polymer contains a polymer selected from the group consisting of polyvinyl alcohol, polyethylene, polypropylene, PVP/polyvinyl propylene, ethylene vinyl acetate, celllulose, carboxymethylcellulose, and polystyrene.

6. A composition according to claim 5, wherein the polymer comprises polyvinyl alcohol A and polyvinyl alcohol B.

7. A composition according to claim 6, wherein the polyvinyl alcohol A and polyvinyl alcohol B are each present at about 1 to 20%, on a wet weight basis with respect to the total composition.

8. A composition according to claim 7, wherein the ratio of polyvinyl alcohol A: polyvinyl alcohol B ratio is about 3:2.

9. A composition according to claim 8, wherein the alcohol comprises a lower alkyl alcohol.

10 A composition according to claim 9, wherein the lower alkyl alcohol is selected from at least one of the group consisting of methanol, ethanol, *n*-propanol and *I*-propanol.

11. A composition according to claim 10, wherein the alcohol contains ethanol.

12. A composition according to claim 4, wherein the pharmaceutical agent is an agent selected from the group consisting of: an anti-inflammatory, a local anesthetic, a xanthine derivative, an antihistaminic, an antifungal, an antimicrobial, an antibiotic, a cardiovascular, a hormone, an erectile dysfunction treatment, a vasodilator, an antirheumatoid, a chemotherapy, an adrenergic agonist or an adrenergic antagonist.

13. A composition according to claim 4, wherein the pharmaceutical agent is a non-steroidal anti-inflammatory agent.

14. A composition according to claim 4, wherein the pharmaceutical agent is an anti-infective agent.

15. A composition according to claim 14, wherein the anti-infective agent is an agent selected from the group consisting of an anti-viral, an anti-bacterial, an anti-fungal, and an anti-parasitical agent.

16. A composition according to claim 4, wherein the pharmaceutical agent is a local anesthetic.

17. A composition according to claim 15, wherein the anesthetic is lidocaine base.

18. A composition according to claim 4, wherein the cosmetic agent is one or more selected from the group of agents consisting of: anti-irritant, anti-oxidant, skin conditioning, anti-blotching, anti-aging, anti-cellulite, skin firming, eye contour, slimming, sooth, sun burn, skin lifting, anti-elastase, anti-collagenase, free radical scavenger, seboregulator, hydrative, vitamin, mineral, α-hydroxy acid, and anti-hyperpigmentation agents.

19. A composition according to claim 18, wherein the anti-hyperpigmentation agent is selected from the group consisting of Melawhite, Biowhite™, Etioline, Arbossa, Gatuline whitening, Ascorbocilan C, and kojic acid.

20. A composition according to claim 4, wherein the cosmetic agent is an anti-irritant.

21. A composition according to claim 20, wherein the anti-irritant is selected from the group consisting of α-bisabolol, camomile, tea tree (*Melaleuca alternifolia*) oil, green tea (*Camellia sinensis*) extract, aloe (*Aloe vera*) extract, licorice (*Glycerrhiza glabra*) extract, glycyrrhetinic acid, witch hazel (*Hamamelis virginiana*) extract, and glycerol.

22. A method for delivering an active agent to the skin of a subject, comprising:

(i) combining a polymer mixture, an active ingredient mixture;

(ii) adding an alcohol mixture to the mixture in step (i) to form a composition; and

(iii) applying the composition to the skin of the subject for delivery of the active ingredient to the skin.

23. A method according to claim 22, wherein the step of applying the composition to the skin of the subject further comprises: selecting a method of application from the group consisting of: spraying from a container; pressing from a tube, spreading from a rollette, and pumping from a jar with an apical manual pump.

24. A method according to claim 23, wherein step (ii) further comprises : removing air bubbles under conditions of ambient temperature and pressure.

25. A method according to claim 24, wherein removing the air bubbles comprises placing the composition under conditions of reduced atmospheric pressure.

26. A method according to claim 23, wherein the container is selected from the group consisting of an aerosol can, an atomizer, a tube, a rollette applicator system, and a bottle having an apical manual pump.

27. A composition according to claim 7, wherein the polyvinyl alcohol A and polyvinyl alcohol B are each present at about 1 to 10%, on a wet weight basis with respect to the total composition.

28. A composition according to claim 27, wherein the polyvinyl alcohol A and polyvinyl alcohol B are present at about 6 to 8% and 4 to 5%, respectively, on a wet weight basis with respect to the total composition.

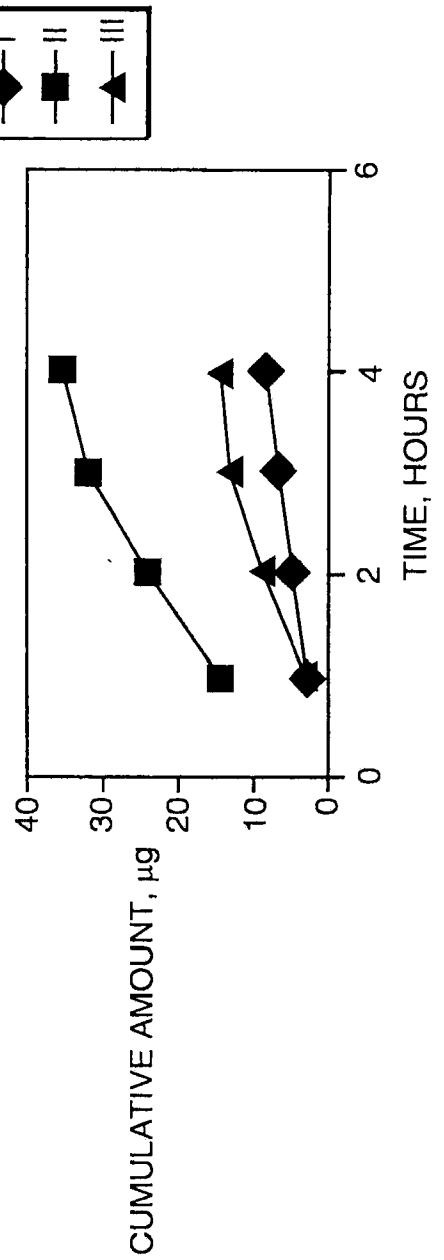

FIG. 1

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/US 00/08428

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/10 A61K47/32 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 58628 A (MARY KAY INC.) 30 December 1998 (1998-12-30) claim 1 page 5, paragraph 5 -page 6, paragraph 1 page 7, paragraph 3 -page 8, paragraph 1 page 9, paragraph 4 -page 10, paragraph 2 page 12, paragraph 2 ---	1-5,9, 10,12, 13,16-28
X	GB 1 108 837 A (ASTRA) claims 1-5 page 5; example 2 page 6, line 51 - line 91 --- -/--	1-5, 9-12,16, 17,22-26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2000	08/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

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PCT/US 00/08428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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